RESCUE PERCUTANEOUS CORONARY INTERVENTION: DOES THE CONCEPT MAKE SENSE?

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Rescue percutaneous coronary intervention (PCI) for ST elevation myocardial infarction (STEMI) is defined as mechanical reperfusion for failed fibrinolysis. The efficacy of rescue PCI has always been debated. Despite a high level of immediate technical success and the positive impact on ventricular function, conflicting data on mortality have been reported. Several historical explanations may be given. Initially, rescue PCI was associated with a high reocclusion rate and increased mortality if unsuccessful. Contrary to fibrinolysis, the rare randomised trials on rescue PCI are characterised by small study populations and major differences in methodology. In particular, there is no consensus on timing and defining failed fibrinolysis. During the last few years two randomised trials, both from the UK, have been published, providing new insights into this old problem. It is now apparent that rescue PCI is superior to conservative management or pharmacotherapy. Efforts should be made to implement this treatment in patients who fail fibrinolysis.

HISTORICAL BACKGROUND

STEMI is a dramatic clinical condition and a major healthcare problem. However, changes in the management of STEMI over the past two decades are a perfect illustration of how progress in medicine has the potential to improve prognosis. Not until the early 1980s, following the publication of the pioneering paper by De Wood *et al* on coronary thrombosis, was the principle of reperfusion recognised and accepted as the rule.[1] Consequently, fibrinolytic therapy became the treatment of choice. At present, this treatment is still widely applied and supported by a large body of scientific evidence. Fibrinolysis is especially effective within 2 h of symptom onset and is still the primary treatment in rural areas without a ''network of referral for mechanical reperfusion''. Percutaneous reperfusion (referred to as primary PCI), introduced more than 15 years ago, has nowadays become the preferred strategy, particularly as its benefit extends beyond the optimal ''3 h'' therapeutic window of fibrinolysis.[2] Recent European and US scientific guidelines clearly state the place for each treatment option, pending on the time of presentation, the door-to-balloon time, and the experience of the operator and the centre.

From the early days of reperfusion, failure of fibrinolysis was identified and patients were occasionally taken to the catheterisation laboratory (cath lab). The concept of ''rescue PCI'' was born. According to Webster's dictionary the term ''rescue'' means to deliver from danger or evil. In medical terms the dictionary defines this verb as an act that saves lives. But does rescue PCI improve prognosis? The answer to this question is still pending.

THE ''OPEN ARTERY HYPOTHESIS''

Prompt restoration of epicardial blood flow of the infarct-related artery within the time frame of myocardial viability, defined as the ''open artery hypothesis'', is a generally accepted concept. Without any exception, all the large randomised trials on fibrinolysis have shown that timely reperfusion reduces acute adverse events and improves long-term clinical outcomes.[2] Beyond this principle, it became quickly apparent that reperfusion needed to be assessed at the epicardial or, more specifically, at the myocardial level. Initially, angiographic substudies on fibrinolysis introduced the TIMI (Thrombolysis in Myocardial Infarction) grade flow as a marker of epicardial perfusion in 1987 (the TIMI scale ranges from grade 0 (occlusion) to 3 (normal or equivalent to a non-culprit artery)). These substudies indicated that a TIMI 3 flow was correlated with improved survival and that even a slight reduction to grade 2 significantly reduced prognosis.[3] Over time, the optimal assessment of reperfusion has been shifting further down to the microvascular and myocardial level. Increasing experience with primary PCI (which enabled immediate angiographic analysis) disclosed a potential discordance between the TIMI flow and the quality of perfusion at the myocardial level. It has been

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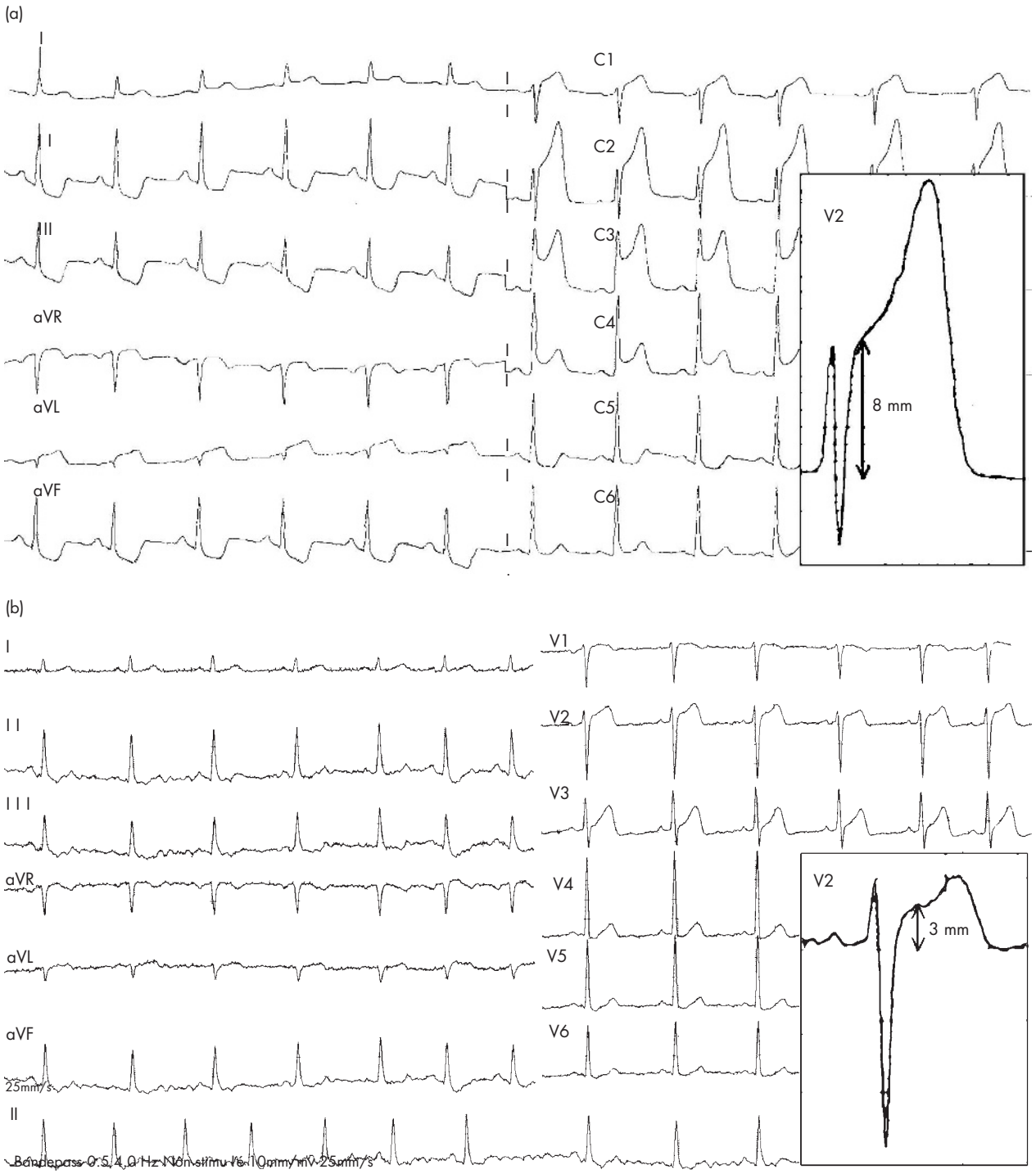

Figure 1 Practical demonstration of the ST segment resolution score (STR) in a patient treated by fibrinolysis for an acute anterior myocardial infarction. (A) ECG on admission. The maximum ST segment elevation is observed in lead V2 (8 mm). (B) ECG performed 90 min after fibrinolysis. Now the maximum ST segment elevation is only 3 mm, implying an STR above 50%.

estimated that about 40% of patients with normalised TIMI flow do not achieve microvascular integrity.[4]

Obviously, a first and easily identifiable marker of myocardial reperfusion was the resolution of ST segment elevation (STR). Schroder and colleagues proposed in 1994 the following classification: complete (>70%), partial (30–70%), and absent (<30%) STR.[5] At present, this classification is not generally accepted, as a cut-off value of 50% for complete STR has been proposed by other authors. Figure 1 illustrates a case of successful STR. In the cath lab several diagnostic tests have been suggested.[4] Intracoronary Doppler with a 0.014 inch steerable Doppler tipped wire enables analysis of epicardial coronary velocities as a surrogate for microvascular perfusion. The corrected TIMI frame count is an objective measure of

epicardial flow progression beyond a standardised coronary landmark, contrary to the visually assessed TIMI flow. The exact speed of digitised images of angiographic film is standardised and is therefore used to calculate the frame count. The myocardial blush grade is a surrogate marker of myocardial perfusion as the contrast blush intensity indirectly quantifies the myocardium distal to the "mother" artery. The blush score varies from 0 (absence of blush, only visualisation of the coronary artery) to 3 (full greyish filling of the muscle distal to the epicardial artery). Figure 2 illustrates the blush score in a patient treated by primary PCI for inferior myocardial infarction. Failure to reperfuse leads to myocardial necrosis. Therefore, a number of tests are based on quantification of infarct size. Myocardial scintigraphy, contrast echocardiography and magnetic resonance imaging (in chronological order of appearance over time) allow precise measurements of the percentage myocardium of the left ventricle involved and/or the total weight of myocardial necrosis.

From a practical point of view, immediately after reperfusion therapy, STR seems the most appropriate means to assess myocardial perfusion. Moreover, STR can be monitored permanently in the coronary care unit. Magnetic resonance imaging emerges as the most promising technique on follow-up because of its precision and future technical developments.

A few co-indicators of successful reperfusion have not been advocated until now. Clinical parameters such as chest pain relief, reperfusion arrhythmia and haemodynamic improvement are extremely useful in the final judgement of reperfusion, but lack accuracy if assessed solely. Biochemical markers are of limited value because of the time constraint of rescue interventions.

A brief reminder of these diagnostic tools is essential to provide insight into the design and limitations of trials on rescue PCI (box 1). There is no uniform definition of failed fibrinolysis in *any* of the few randomised trials of rescue PCI. This definition is closely linked to trial end points based on the above diagnostic tests. Furthermore, there is a thin line between rescue PCI, systematic PCI after fibrinolysis, and facilitated PCI (box 2). Finally, these different strategies have been on trial together with primary PCI.

RESCUE PCI ON TRIAL

Rescue PCI has often been included in a global strategy of reperfusion and therefore clinical research confined to the rescue concept only has remained scarce. Furthermore, selection bias, inconclusive outdated early observational trials, and subsequent lack of interest for the subject have created a common opinion between interventional cardiologists that rescue PCI was rather a "conscience tranquilliser" than a clinically useful procedure.

Rescue angioplasty in the early days

From 1986 on, the clinical outcome of patients who failed reperfusion in the large fibrinolysis trials (GUSTO, TAMI, TIMI) and who were treated by rescue PCI was reported. The major observations were high reocclusion rates and a 39% mortality in case of failed rescue PCI. In 1992, a pooled analysis of early experiences indicated a 18% reocclusion rate and an overall mortality of 10.6%. Because of the tremendous progress in angioplasty technology and pharmacotherapy, these results are only of historical interest.

Rescue PCI as a part of larger randomised trials

Historically, the TAMI-5 trial was the first prospective study that included rescue PCI as part of the study design.[6] Patients treated with thrombolytic agents were randomised to an aggressive strategy with rescue PCI if needed versus a deferred, ischaemia driven strategy. The indication for rescue PCI was TIMI flow 0 or 1 and was performed in 18% of the aggressive strategy group without increased side-effects. The major findings were a high infarct-related artery patency (96%) and improved outcomes in terms of regional wall motion, recurrent ischaemia and mid-term vessel patency.

A pilot trial from the south-east part of the Netherlands initially investigated three different reperfusion strategies for acute myocardial infarction: (1) fibrinolysis in a local hospital; (2) immediate transfer after fibrinolysis to a tertiary centre with rescue PCI in case of TIMI 0 or 1 flow; and (3) transfer for primary PCI.[7] Transfer was shown to be feasible and safe but, because of the small study population, there were no differences in primary outcome measures.

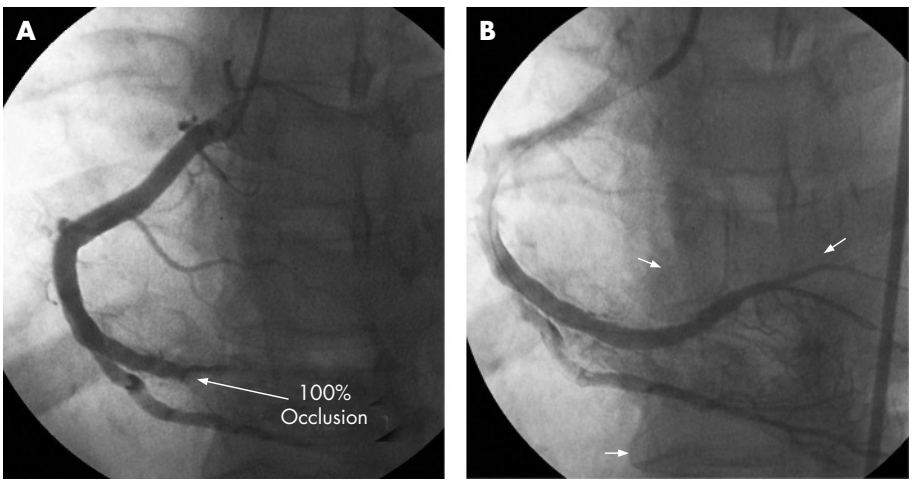

Figure 2 Demonstration of the myocardial blush score during primary percutaneous coronary intervention (PCI) in a patient with an acute inferior myocardial infarction. (A) Diagnostic image of the right coronary artery on selective coronary angiography showing total occlusion of the mid portion of this vessel. (B) Final image after PCI and stenting demonstrating a full greyish blush in the muscle distal to the epicardial artery.

Box 1: Tests of myocardial reperfusion

- ECG: ST elevation resolution
- Angiography:
  - corrected TIMI frame count
  - myocardial blush grade
  - intracoronary Doppler measures
- Infarct size quantification:
  - Tc99m sestamibi nuclear imaging
  - myocardial contrast echocardiography
  - magnetic resonance imaging

Box 2: Defining PCI in myocardial infarction

- **Rescue PCI:** PCI for failed fibrinolysis
- **Systematic PCI:** immediate PCI after fibrinolysis
- **Facilitated PCI:** PCI after reperfusion pharmacology not limited to fibrinolytics only
- **Primary PCI:** mechanical intervention for acute myocardial infarction

The PRAGUE trial conducted in the Czech Republic had a similar design, with the only difference that rescue PCI was also performed for TIMI 2 flow.[8] The decision to intervene for TIMI 3 flow was left at the discretion of the operator. Therefore, rescue PCI was performed in 82% of cases in group 2. The composite end point (death, myocardial infarction and stroke at 30 days) was reached in 23%, 15% and 8%, respectively ($p<0.02$). This trial was the first to demonstrate the efficacy of transfer for primary PCI.

Rescue PCI has always been part of trials on systematic and facilitated PCI. Nevertheless, it has never been studied as precociously as in the above three trials. This can be illustrated by referring to the historical extremes on facilitated PCI: the SAMI (1992) and ASSENT-4 (2006) trials.[9 10] The SAMI trial randomised 122 patients to primary PCI or systematic PCI after fibrinolysis with streptokinase.[9] In the streptokinase group, the drug had been administered *after* angiography in 40% of patients, making any interpretation of the results impossible. The ASSENT-4 trial intended to randomise 4000 patients to primary or facilitated PCI with tenecteplase.[10] The trial was prematurely stopped at 1667 patients because of an excess in in-hospital mortality in the facilitated group (6% vs 3%, $p = 0.0105$). In this group the TIMI 3 flow was 43% and, according to protocol, the large majority (93%) of these patients was stented. Overall, the composite end point of death, congestive heart failure and shock at 90 days was more frequent in the facilitated group (19% vs 13%, $p = 0.0045$).

The results of ASSENT-4 contrast with another recent trial. Indeed, the publication of GRACIA-1 in 2004 had shifted the facilitated PCI debate again in favour of the latter as patients randomised to systematic angiography and possibly PCI within 24 h after fibrinolysis fared better than patients who were treated conservatively.[11] The difference in outcome was explained by a lesser need for revascularisation. Stent use was 80%, and 32% of patients received abciximab in the invasive arm of GRACIA-1, indicating the contemporary setting of this trial. Importantly, this strategy did not increase major bleeding rates. The study concept was certainly different from ASSENT-4 as a conservative approach and not primary PCI was on trial, but at least facilitated PCI within 24 h appeared safe and effective. In ASSENT-4, glycoprotein IIb/IIIa antagonists were only allowed in bailout situations and therefore only 10% of patients in the facilitated group received them. Several other issues concerning ASSENT-4 have been raised by the authors: (1) A medium time beyond the "golden" 2 h between symptom onset and fibrinolysis in the majority of patients and a medium interval of 104 min between tenecteplase administration and the first balloon inflation—the authors considered this interval relatively short and probably insufficient to allow the thrombolytic drug to act. (2) The protocol did not allow pre-treatment with clopidogrel and glycoprotein IIb/IIIa antagonists in the facilitated group—at the time of the study design, safety concerns and lack of clinical data had prevented the investigators from doing so.

The above trials have been integrated in a meta-analysis on 17 trials on facilitated PCI by Keeley *et al*.[12] Their conclusions are equivocal: facilitated PCI offers no clinical benefit and should be avoided, particularly with thrombolytic agents. Is this statement a bridge too far? The answer is probably yes. First, a large trial on facilitated PCI (combining fibrinolytics and glycoprotein IIb/IIIa antagonists), the FINESSE trial, is still ongoing and, contrary to ASSENT-4, has not been stopped by its safety committee. Secondly, this meta-analysis has several important limitations essentially related to a lack in homogeneity. The analysis included early historical trials that do not reflect contemporary good clinical practice. Furthermore, besides the lack of key information on timing intervals and long-term clinical follow-up, there is important heterogeneity in study end point and trial design.

At present, it can be concluded that systematic and, in particular, urgent PCI after fibrinolysis cannot be recommended. Angiography and PCI, if indicated the day following fibrinolysis (according to the 24 h concept of GRACIA-1), may be performed as it is safe (without increased bleeding) and effective in reducing the need for revascularisation. Finally, the results of the FINESSE trial are eagerly awaited.

Rescue PCI trials

Belenkie *et al* were the very first to study rescue PCI in a randomised pilot trial in 28 patients.[13] The only relevant conclusion of this study, published in 1992, concerned mortality: during hospitalisation, one patient died in the PCI group, while four did not survive in the conservative arm.

RESCUE 1, conducted between 1990 and 1993, was the first "true" rescue PCI trial.[14] A total of 151 patients with anterior myocardial infarction and persistent TIMI 0 or 1 flow after lytic therapy were randomised to PCI or medical treatment. The

Facilitated PCI: key points

- Systematic, unconditional angiography and in particular PCI performed *within hours* after fibrinolysis is obsolete
- Angiography, and PCI if the anatomy is suitable, performed *the day after* fibrinolysis is safe and reduces the need for subsequent revascularisation
- The place of facilitated PCI (combining fibrinolysis and glycoprotein IIb/IIIa antagonists) is still under investigation
- Facilitated PCI is not recommended outside the context of randomised trials

primary end point (30 day ejection fraction measured by scintigraphy with exercise) was higher after PCI compared to medical treatment (43% vs 38%, respectively, p = 0.04). The secondary end points were 30 day mortality, heart failure (New York Heart Association functional class III or IV), and ventricular tachycardia beyond 48 h of infarct onset. In a composite manner, no significant difference was observed (17.9% vs 27.8%, respectively, p = 0.31). However, the combination of mortality and heart failure significantly favours rescue PCI (6.4% vs 16.6%, respectively, p = 0.05).

In 1995, the RESCUE study group initiated the RESCUE II trial.[15] The study hypothesis was based on the evolving concept of optimal myocardial reperfusion and therefore an angiographic entry criterion of TIMI 2 flow was defined for rescue PCI. Only 29 patients were studied in this trial that was never terminated and fully published. The results were inconclusive and will therefore not be discussed.

Between 1995 and 2000, the interventional community focused on improving the logistics and the emerging concept of inter-hospital transfer for primary PCI. In 1999, however, two large multicentre trials were launched simultaneously in the UK on rescue PCI. The MERLIN and REACT trials were conducted over a time period of 3 and 5 years and published in 2004 and 2005, respectively. They have considerably improved current knowledge.

The MERLIN trial, confined to the Middlesbrough region, randomised 307 patients with persistent 50% ST segment elevation 60 min after fibrinolysis to rescue PCI or conservative management.[16] All cause mortality at 30 days (which was the primary end point) did not differ between the two groups (9.8% vs 11%, respectively, p = 0.7). The secondary end point (which was a composite of mortality, reinfarction, stroke, revascularisation and heart failure at 1 month) occurred less frequently in the rescue group (27.3% vs 50%, p = 0.02), mostly because of a lesser need for revascularisation. Nevertheless, stroke and the need for transfusion were more common after PCI (4.6% vs 0.6%, p = 0.03, and 11.1% vs 1.3%, p<0.001, respectively).

The REACT trial is the largest and most accurate trial on rescue PCI.[17] This nationwide trial compared rescue PCI with repeated fibrinolysis and conservative care in 427 patients. PCI was performed for a TIMI flow <3 and lesion >50%. The primary objective (a composite end point of all cause mortality, recurrent infarction, stroke and heart failure at 6 months) was achieved. This adverse event rate was 15.3%, 31% and 29.8%, respectively (p<0.01). Here, the main reason for the lower rate in the rescue PCI group was a lower recurrence of myocardial infarction.

A critical analysis of the MERLIN trial raises several major concerns. First, the study was clearly underpowered to achieve the primary mortality end point. Second, randomisation occurred too early at 60 min according to current knowledge. Third, the use of stents (50.3%) and glycoprotein IIb/IIIa antagonists (3.3%) was remarkably low. Finally, the reported mortality was unusually high. Objectively, from a methodological point of view, the MERLIN trial is a study on urgent systematic PCI rather than classical rescue PCI. As discussed previously, systematic urgent PCI after fibrinolysis has become obsolete.

The design of REACT was fundamentally different and successful by anticipating more accurately the evolution in interventional cardiology. A classical composite end point was chosen, although fixed at 6 months rather than 1 month. Randomisation was performed at 90 min, leaving time for the lytic agent to act. The three-arm design allowed the study to investigate the efficacy of a second fibrinolysis. Although the trial was prospectively not powered to detect differences in survival, a trend towards a lower 6-month mortality was detected with rescue PCI (6.2%) compared to repeat fibrinolysis (12.7%) and conservative treatment (12.8%) (p = 0.12). Stent implantation (68.5%) and glycoprotein IIb/IIIa antagonist administration (43.4%) reflect current practice without, for the latter, any negative impact on the safety of the procedure. In summary, REACT is a mature, well-designed trial demonstrating the safety and efficacy of rescue PCI and a definite trend towards a lower mortality. Putting this trial into a broader perspective, only meta-analyses and very long-term follow up studies on *primary PCI* have made it possible to demonstrate a positive impact on such a hard end point as mortality. Finally, most trials have suffered from funding issues because of lack of interest from the industry in the rescue PCI concept.

Observational trials on rescue PCI

There is an abundance of observational data on rescue PCI. A few reports merit attention. Globally, rescue PCI patients have a higher clinical risk profile and suffer from the time delay between diagnosis of reperfusion failure and PCI, in particular if transfer to a tertiary centre is required.[18] Only if admitted directly to a tertiary centre and adequately diagnosed at 90 min, and promptly treated, is their clinical course comparable to those patients successfully reperfused by fibrinolysis.[19] Finally, a very recent observation in 214 patients, treated rapidly but also aggressively (thrombectomy 21%, intra-aortic balloon pump 17%, glycoprotein IIb/IIIa antagonists administration 92%), demonstrated an in-hospital mortality of only 3.4%.[20] Obviously, the retrospective bias of these observations cannot concur with adequate randomised controlled trials, but they provide a few clear and practical recommendations. Efforts should be made to shorten time delay and improve logistics, as in the case of transfer for ''routine'' primary PCI. Patients receiving fibrinolysis and directly admitted to a hospital with cath lab facilities should undergo immediate rescue PCI if appropriate, once the 90 min time delay has been reached. In patients admitted to local hospitals, potential failure of fibrinolysis should be anticipated by communication with a tertiary centre from 60 min on to enable immediate transfer at 90 min in case of persistent ST elevation.

Stent implantation should be unconditional, aiming for an optimal angiographic result. Glycoprotein IIb/IIIa antagonists

Rescue PCI: key points

- Patients with persistent >50% ST elevation 90 min following fibrinolysis should undergo rescue PCI
- Rescue PCI has a significant impact on the recurrence of myocardial infarction and reduces the need for subsequent revascularisation
- At present, only a trend towards reduced mortality has been demonstrated
- Optimal logistics are crucial, particularly for those patients admitted to local hospitals

do not seem contraindicated despite prior fibrinolysis, but careful monitoring of anticoagulation is required.

UNRESOLVED ISSUES

Primary PCI has been studied extensively for subgroups of patients (elderly, women) and clinical risk score models such as the TIMI risk score. Furthermore, the efficacy of primary PCI has now also been studied beyond the therapeutic window of 12 h after symptom onset. No conclusive information is available in the setting of rescue PCI. Currently no specific recommendation can be given for the older patient, the clinical low risk patient, or the patient presenting late without any sign of reperfusion. Importantly, the latter condition should not be confounded with the GRACIA-1 type scenario. If in doubt, angiography should always be performed, and PCI if appropriate (TIMI flow <3 and a lesion >50%).

PRACTICAL RECOMMENDATIONS AND CONCLUSIONS

Figure 3 provides a pragmatic algorithm to guide clinicians in rescue PCI. Essentially, prompt recognition of failed fibrinolysis, anticipation of time delays and rapid transfer to the cath lab are the initial steps to be undertaken. It is essential to assess the ST segment resolution at 60 min independent of the availability of a cath lab facility. In a tertiary centre, the cath lab team can be alerted to start PCI on time at 90 min if ST resolution persists. Regional hospitals without a cath lab should also anticipate failure from 60 min on. Hospitals located more than 60 min from a cath lab site should consider transfer for persistent ST elevation at this time so as not to exceed the 120 min PCI time window. Even if ST segment resolution occurs, angiography and PCI can be planned semi-electively. Those hospitals situated within a closer range should also alert the cath lab team and transfer immediately at 90 min.

Within the lab, the administration of glycoprotein IIb/IIIa antagonists is recommended. The use of unfractionated heparin is recommended as it enables precise adjustment according to activated clotting time not to exceed 250 s. There are insufficient data to support the use of low molecular weight heparin in this setting. Stenting should be performed according to standard practice. Following PCI, management should not differ from classical post-myocardial infarction care: mobilisation, patient education and secondary prevention. Nevertheless, these patients remain at higher risk and therefore particular attention should be given to the extent of myocardial necrosis and consequent left ventricular function to anticipate and treat mid- and late-term complications. Time has come to consider rescue PCI no longer as a ''conscience tranquilliser'' but as a clinically justified act to improve the health of our patients.

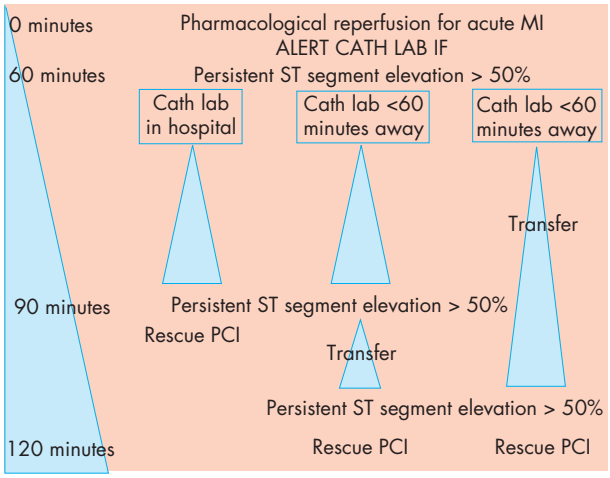

Figure 3 Practical algorithm for rescue percutaneous coronary intervention (PCI). On the left hand side the evolving time is depicted. The primary initiative is fibrinolysis for acute myocardial infarction. The ECG is the key decision tool. The algorithm is built for persistent ST elevation and the potential need for rescue PCI. In case of adequate ST resolution, angiography and/or PCI *should not* be performed.

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